Office Action Summary	Application No.	Applicant(s)	
	10/585,566	MOSCHEL ET AL.	
	Examiner	Art Unit	
	Cecilia M. Jaisle	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17,31,32,40,41 and 49-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-15 and 49-58* is/are allowed.

6)☒ Claim(s) *16,17,31,32,40,41 and 59-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Supplemental Office Action

The Supplemental Office Action is issued to consider the Applicant's Response of Nov. 14, 2008 which crossed in the mail with the Non-Final Rejection of Nov. 20, 2008. The Office Action of Nov. 20, 2008 is withdrawn in favor of the present Office Action and a new period of response is set to start with the date of mailing of the present Office Action. Since the Index of Claims and Search Notes remain the same, these documents are not included with this Office Action.

Restriction

The election of Group I claims 1-15 and 49-58 is acknowledged. Claims 16, 17, 31, 32, 40, 41 and 59-64 are withdrawn as directed to non-elected subject matter. Claims 16, 17, 31, 32, 40, 41 and 59-64 are subject to rejoinder if elected claims 1-15 and 49-58 are found to be allowable.

Rejoinder

Claims 1-15 and 49-58 are directed to an allowable product. Following is an examiner's statement of reasons for allowance. These claims were previously rejected in the Office Action of Nov. 15, 2007 over McMurry, et al., US 5929046, issued Jul. 27, 1999. The claims were amended in the Response of Feb. 1, 2008 to avoid McMurry. In addition, claims 1-15 and 49-58 are neither anticipated nor obvious over any of the other prior art of record, whether taken individually or in any combination.

Pursuant to the procedures set forth in MPEP § 821.04(b), claims 16, 17, 31, 32, 40, 41 and 59-64, directed to the process of using the allowable product, previously withdrawn from consideration as a result of a restriction requirement of Nov. 15, 2007, are hereby rejoined and fully examined for patentability under 37 CFR 1.104.

Because a claimed invention previously withdrawn from consideration under 37 CFR 1.142 has been rejoined, **the restriction requirement between Groups I and III as set forth in the Office action mailed on Nov. 15, 2007 is hereby withdrawn**. In view of the withdrawal of the restriction requirement as to the rejoined inventions, applicants are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Once the restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Rejections Under 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16, 17, 31, 32, 40, 41 and 59-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inactivation of human O^6-alkylguanine-DNA alkyltransferase *in vitro*, does not reasonably provide enablement for:

- a method of enhancing the chemotherapeutic treatments of tumor cells in a mammal with an antineoplastic alkylating agent that causes cytotoxic lesions at the O^6-position of guanine comprising co-administering a compound or salt of claims 1, 5 or 9 and an antineoplastic alkylating agent which causes cytotoxic lesions at the O^6-position of DNA guanine residues (claims 16, 17, 59, 62);
- a method for treating tumor cells in a mammal by administering a compound or salt of claim 1 (claims 31, 32, 60, 63);
- a method of inhibiting the reaction of O^6-alkylguanine-DNA alkyltransferase with an alkylated DNA by reacting *in vitro* the O^6-alkylguanine-DNA alkyltransferase with a compound or salt of claim 1 (claims 40, 41, 61 64);

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Many if not most diseases said to be treated by the claimed methods, such as tumor cells and cancer, are known as difficult to treat. Substantiation of utility and its scope is required when utility is "speculative," "sufficiently unusual" or not provided. See *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909 (BPAI 1981). Also, note *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex parte Powers*, 220 USPQ 924 (BPAI 1982) regarding types of testing needed to support *in vivo* uses.

Applicants' attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 66 FR 1092-1099 (2001), emphasizing that "a claimed invention must have a specific and substantial utility." See also MPEP 2163, *et. seq*. This disclosure is not sufficient to enable the claimed methods based solely on the disclosed inactivation of human O^6-alkylguanine-DNA alkyltransferase *in vitro*.

MPEP § 2164.01(a) states:

> A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Many factors require consideration when determining whether sufficient evidence supports a conclusion that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue." MPEP 2164.01(a). These factors include: (1) the claim breadth; (2) the nature of the invention; (3) the state of the prior art; (4) the level of predictability in the art; (5) the amount of direction provided by the inventor; (6) the presence of working examples; and (7) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)(reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). See also *In re Goodman* 29 USPQ2d 2010, 2013 (Fed. Cir. 1993). Application of these factors to the present application supports the determination that the present disclosure fails to satisfy the enablement requirement:

1. **Breadth of the claims:**

(a) Scope of the methods. The claims cover methods using 2-amino-O4-substituted pteridines in treatments as mentioned above.

(b) Scope of the diseases covered. The claims cover treatment methods for all tumor cells. A tumor is a swelling or lesion formed by an abnormal neoplastic growth of cells. Tumor is not synonymous with cancer, but can be benign, premalignant or malignant, whereas cancer is by definition malignant. However, the specification (page 13, *inter alia*) clearly states that "[t]he present invention has applicability to the treatment of any type of cancer capably of being treated with an antineoplastic alkylating agent that causes cytotoxic lesions at the O6-position of guanine."

Cancer includes colon, prostate, brain, breast, ovarian, lung, stomach cancers, lymphoma, leukemia, Wilms' tumor rhabdomyosarcomas, multiplemyeloma, soft-tissue sarcomas, Hodgkin's and non-Hodgkin's lymphomas and many others.

- Colon cancers include many types which are rather diverse. Most are adenocarcinomas, either of the mucinous (colloid) type or signet ring type. Less common colon cancers include squamous cell, neuroendocrine carcinomas, carcinomas of the scirrhous type, lymphomas, melanomas (primary or meta-static), sarcomas (fibrosarcomas and Leiomyosarcomas) and Carcinoid tumors.
- Carcinomas of the prostate are usually adenocarcinomas, but others include small cell carcinoma, mucinous carcinoma, prostatic ductal carcinoma, squamous cell carcinoma of the prostate, basal cell carcinoma, neuro-endocrine carcinoma, signet-ring cell carcinomas and others.

- Breast cancers come in great variety. The most important category of breast cancers is the ductal cancers, which come in a wide variety of types, divided into categories: intraductal (*in situ*); invasive with pre-dominant intraductal component; invasive, NOS; comedo; inflammatory (IBC); medullary with lymphocytic infiltrate; mucinous (colloid) carcinoma; papillary carcinoma; scirrhous; tubular and others. Another category is lobular breast cancers: *in situ*, invasive with predominant *in situ* component and invasive. Paget's disease of the nipple can be also with intraductal carcinoma or with invasive ductal carcinoma. Adenomyoepithelioma is dimorphic tumor characterized by the presence of both epithelial and myoepithelial cells. There is breast angiolipoma and spindle cell lipoma of the breast. There is lymphoma of the breast (both Non-Hodgkin's lymphoma of the breast and Hodgkin's disease of breast forms). There are some sarcomas, including giant cell sarcoma of the breast, leiomyosarcoma of the breast, Angiosarcoma of the breast, cystosarcoma phylloides and liposarcoma of the breast. There are carcinoid tumors that can be primary carcinoid tumors of the breast or can arise from nonmammary sources. There are breast salivary gland-like tumors, including acinic cell carcinoma, oncocytic carcinoma (Mammary epithelial oncocytoma) and mucoepidermoid carcinoma. Other rare carcinomas include Spindle cell carcinoma of the breast, Squamous cell carcinoma of the breast, Secretory Carcinoma of the Breast (Juvenile secretory carcinoma), Metaplastic carcinoma of the breast (a heterogeneous group of invasive breast cancers including types with squamous differentiation and those with heterologous elements), Invasive Micropapillary Carcinoma of the Breast, Adenoid cystic

carcinoma of the breast, cribriform carcinoma, Myofibroblastoma of the Breast (Benign spindle stromal tumor of the breast) and glycogen-rich clear cell carcinoma of the breast. There are numerous other rare breast cancers, including e.g., Fibromatosis of the breast (extra-abdominal desmoid), Angiomatosis of the Breast and mammary hamartoma. There are also nonmammary tumors, primarily adenocarcinomas, that can metastasize to the breast, including bronchogenic carcinomas, malignant melanomas (primary and secondary), rhabdomyosarcomas, malignant mesotheliomas, thyroid carcinomas, renal cell carcinomas, malignant lymphomas and gastrointestinal carcinomas (including those from the stomach, pancreas, esophagus and colon).

The specification fails to identify the results of treatment with the methods of this invention and how such results would be recognized, particularly with regard to conditions and diseases that are currently considered incurable, untreatable or fatal.

2. **Nature of the invention and predictability in the art:** The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

Pharmacological activity in general is unpredictable. In applications involving physiological activity, such as the present:

> The first paragraph of 35 U.S.C. §112 effectively requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

Plant Genetic Systems v. DeKalb Genetics Corp., 65 USPQ2d 1452 (CAFC 2003).

3. **Direction and Guidance:** That provided is very limited. The dosage range information is meager at best. It is generic, the same for all disorders the specification covers. No specific direction or guidance provides a regimen or dosage effective specifically for all of the conditions construed by the claims.

4. **State of the prior art:** The art indicates the need for undue experimentation.

Schold, et al., Neuro-Oncology, Jan. 2004, 28-32, reports only the beginning of clinical trials.

> Although only marginally effective in most cases, drugs that alkylate DNA in the O^6-position of guanine are the agents most commonly used against anaplastic gliomas. These include the nitrosoureas, procarbazine, and temozolomide. Resistance to cytotoxic effects of these agents is mediated in large part by the DNA repair protein O^6-alkylguanine-DNA alkyltransferase (AGT). AGT can be transiently suppressed by the exogenous administration of O^6-benzyl-guanine (BG), which binds to and inactivates the repair protein. During the period of suppression and until new AGT protein is synthesized, the cells in which AGT has been suppressed are dramatically more sensitive to DNA alkylating drugs. Consequently, BG has entered clinical trials in combination with carmustine, a representative alkylating agent.

Javanmard, et al., J. Med. Chem., 2007, Vol. 50, # 21, 5193-5201, summarized limited ability of tested compounds to sensitize cells to alkylating agents:

> Despite the excellent alkyltransferase inactivation activity of the folate esters describe in this paper, their ability to sensitize cells to alkylating agents was limited. This is most likely due to a low level of uptake rather than rapid degradation because their conversion to folate by cellular esterases was quite slow. However, they provide a very useful lead for the design of other highly water soluble, specific, and potent alkyltransferase inhibitors based on the ability to interact with additional residues in the alkyltransferase active pocket.

Thus, ability of an agent that inactivates O^6-alkylguanine-DNA alkyltransferase to treat all diseases recited by the claims remains open to further study and proof.

5. **Working Examples:** Applicants do not provide highly predictive competent evidence or recognized tests to treat all conditions recited for the claims. Furthermore, Applicants have not provided competent evidence that the instantly disclosed tests are highly predictive for all uses disclosed and embraced by the claim language for all of the intended hosts.
6. **Skill of those in the art:** Ishiguro, Schold and Javanmard call into question the efficacy of treatment with the claimed methods. These references discussed above confirm the need for additional research.
7. **Quantity of experimentation needed to make or use the invention.** Based on the disclosure's content, an undue burden would be placed on one skilled in the pharmaceutical arts to use the invention, since the disclosure gives the skilled artisan inadequate guidance regarding pharmaceutical use, for reasons explained above. The state of the art, as discussed in the articles above, indicates the requirement for undue experimentation, particularly with regard to potentially devastating side effects. Thus, the ability of an agent that inactivates O^6-alkylguanine-DNA alkyltransferase to treat all of the diseases construed by the present claims remains open to further study and proof.

See MPEP 2164.01(a), discussed *supra*, justifying the conclusion of lack of enablement commensurate with the claims. Undue experimentation will be required to practice Applicants' invention.

Remarks to Response of 11-14-2008

The Declaration Under 37 CFR 1.132 of Dr. Anthony E. Pegg (hereinafter, Pegg Declaration) is insufficient to overcome the rejection of claims 16, 17, 31, 32, 40, 41 and 59-64 under 35 U.S.C. 112, first paragraph, as set forth above. The following insufficiencies are noted in the Pegg Declaration:

- The Pegg Declaration only tests a single claimed compound, O^4-benzylfolate ("BF"), of Formula I in which R1 is a group of formula II, R2 is hydrogen, and R3 is phenyl.
- The Pegg Declaration only tests a single cancer form, KB tumor xenografts in mice.
- Paragraph 5 of the Pegg Declaration ends with the assertion: "This interval should be sufficient for enhancing the cytotoxic effects of BCNU during which DNA adducts undergo chemical rearrangement and form interstrand crosslinks." But no evidence is provided of the successful testing of this assertion. Declarant has merely assumed the enhancement, not demonstrated it.
- Claims 16, 17, 59 and 62 recite, "A method of enhancing the chemotherapeutic treatment of tumor cells …" The Pegg Declaration does not show enhancement of chemotherapeutic treatment of tumor cells.
- Claims 31, 32, 60 and 63 recite, " A method for treating tumor cells in a mammal comprising administering … a (claimed) compound … and administering … an effective amount of an antineoplastic alkylating agent …" The Pegg Declaration does not coadminister a claimed compound and an antineoplastic alkylating agent.

- Claims 40, 41, 61 and 64 recite, "A method of inhibiting the reaction of O^6-alkylguanine-DNA-alkyltransferase with an alkylated DNA compound comprising reacting *in vitro* the O^6-alkylguanine-DNA-alkyltransferase with the (claimed) compound …" The Pegg Declaration does not show inhibition of this reaction.

Claim 40 has presently been amended to recite an *in vitro* process. It was previously assumed to be referring to an *in vivo* process, since that is what would be potentially useful.

Applicants also submit that Ishiguro, cited by the Examiner in the previous Office Action, appears to support Applicants' position. However, note the even more recent article by Hegi, et al., J. Clin. Oncol., Vol. 26, # 25 (Sep. 1), 2008: pp. 4189-4199, discussing correlation of O^6-methylguanine methyltransferase (MGMT) promoter methylation with clinical outcomes in glioblastoma and clinical strategies to modulate MGMT activity, which states that systemic application of MGMT inhibitors is limited by a hematologic toxicity increase, and not all glioblastoma patients having MGMT promoter methylation respond to alkylating agents, and even those who respond will inevitably experience relapse:

> "A variety of molecular markers may have prognostic value in patients with malignant glioma. These markers include high expression of MGMT, overexpression of the epidermal growth factor receptor, presence of the epidermal growth factor receptor vIII mutation, expression of the *YKL-40* gene, tenascin expression, loss or mutation of the *PTEN* gene, loss of chromosome 10, and mutation or loss of the *p53* gene. Although MGMT expression seems to have a strong influence on response to alkylating agents and clinical outcome in patients with GBM, to date none of these markers, including MGMT, has been definitively confirmed.
>
> ....

> Although differences in *MGMT* promoter methylation may determine the clinical course in patients with GBM (glioblastoma) treated with temozolomide, it is presently not recommended to use the *MGMT* promoter methylation assay to determine who should receive temozolomide and who should not. First, an independent confirmation of the retrospective analysis from the EORTC (European Organisation for Research and Treat-ment of Cancer)/NCIC (National Cancer Institute of Canada) trial is necessary. Second, there is reason to believe that alternative dose-intensified schedules may overcome resistance in patients with an unmethylated *MGMT* promoter. Third, allocating patients with GBM to specific treatments on the basis of *MGMT* promoter methylation status will only assume clinical relevance when effective alternative treatments become available. At present, the only established alternative is nitrosourea-based chemotherapy, which is also subject to resistance mediated by MGMT. A promising strategy to overcome resistance mediated by MGMT seems to be depletion of MGMT by prolonged exposure to low doses of alkylating agents. For these agents, the feasibility of intensified dosing schedules has been demonstrated. Optimizing this approach in conjunction with modulation of dosing schedules is of paramount imporance to maximize the clinical effectiveness of temozolomide. However, myelosuppression continues to be dose limiting when MGMT depletion is maximized by dose intensification or the addition of MGMT inhibitors such as O^6-BG (O^6-benzylguanine). The development of tumor-specific MGMT inhibitors may overcome this limitation. This is an area of intense ongoing research, which will hopefully result in further improvements in clinical outcomes."

Accordingly, the non-enablement rejection is proper and is maintained.

Allowed Claims

Claims 1-15 and 49-58 are directed to an allowable product. Reasons for allowing these claims are found earlier in this Office Action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cecilia M. Jaisle, J.D. whose telephone number is 571-

272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Cecilia M. Jaisle

12/9/2008

/James O. Wilson/

Supervisory Patent Examiner, Art Unit 1624